An Investigation of the Protective Influence of Dates Fruit Against Nephrotoxicity in Wistar Albino Rats Induced by Gentamicin

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Article

An Investigation on the Protective Effect of Date Fruit against Nephrotoxicity in Wistar Albino Rats Induced with Gentamicin

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Abstract: Nephrotoxicity is a common adverse effect associated with gentamicin administration. The current study investigated the potential protective effects of date fruit against gentamicin-induced renal nephrotoxicity in female albino rats. Date fruit antioxidants were measured using a spectrophotometer, and GC-MS was performed using a Perkin Elmer Clarus 600 GC and a Turbomass mass spectrometer. Thirty experimental animals were assigned at random to one of three prevention and treatment subgroups. Gentamicin (GM) administration at a dose of 100 mg/kg resulted in renal toxicity, as evidenced by test results showing alterations in kidney function and histological changes in the proximal convoluted tubules. Date fruit improved kidney function (albumin, total protein, uric acid, urea, creatinine) and tubule histology, according to the findings. The GC-MS analysis revealed the presence of 20 chemicals. Date fruit antioxidants included 14 mg/gallic acid total phenolic content, 32.22 mg/rutin equivalent total flavonoid content, and 1000 ug/mL DPPH free radical scavenging. According to the study, date fruit and gentamicin combined performed the best in improving kidney function and histology. Date fruit had a significant impact on prevention during gentamicin treatment.

Keywords: protective; date fruit; nephrotoxicity; female; albino rats; gentamicin

1. Introduction

The kidney is susceptible to drug-induced injury as a result of its elevated relative blood flow [1]. Nephrotoxicity, or renal toxicity, may be due to hemodynamic alterations, cellular and tissue damage, inflammatory tissue injury, or hindrance to renal excretion [2]. Various medicinal medications and environmental contaminants commonly cause nephrotoxicity [3].

The administration of some medications, such as gentamicin and cisplatin, to laboratory animals results in a notable decrease in renal blood flow and glomerular filtration, accompanied by an elevation in vascular resistance [4]. Drugs, whether natural or semisynthetic, cause side effects in the user; this is especially the case for antibiotics such as gentamicin, which is associated with nephrotoxicity and nonoliguric acute renal failure when given for treating Gram-negative bacteria [5]. These effects may manifest without causing chronic morphological alterations in the glomerulus and are not contingent upon tube injury [6]. Gentamicin, an antibiotic from the aminoglycoside class, is widely recognized as a prominent contributor to drug-induced nephrotoxicity [7]. The risk of

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gentamicin nephrotoxicity has decreased in recent years after the once-daily dose regimen and elimination of established risk factors were implemented [8]. Compared with other antibiotics, gentamicin is associated with more severe adverse reactions. Despite gentamicin's success in treating infections, its nephrotoxic effects must be mitigated in order to ensure its continued widespread clinical use [9]. Gentamicin enhances the stimulation of platelet activation factor, resulting in an effect on kidney function [10]. The kidneys are anatomical structures that are normally sited between the T 12 and L13 vertebrae, are bean-shaped, and weigh about 150 g in males and 135 g in females [11]. They have important functions, including balancing water in blood, pH regulation, and filtration and excretion of all metabolic waste products; also, many waste products, such as urea and salts, pass through the kidney nephrons to then be sent to the bladder. Moreover, the kidneys can remove toxic materials and radioactive materials [12].

The administration of gentamicin resulted in nephrotoxicity, as indicated by significant increases in blood urea nitrogen, serum urea, serum uric acid, and serum urea nitrogen (107.51–16.92 mg/dl, 0.89–0.99 mg/dl, 3.05–0.29 mg/dl, and 47.8–9.07 mg/dl, respectively) in comparison to the saline-treated groups. The administration of gentamicin in conjunction with an extract of *Pimpinella anisum* resulted in a dose-dependent reduction in the increase in these parameters. In rats treated with gentamicin, histopathological examination unveiled severe granular degeneration accompanied by epithelial loss. In contrast, the administration of an aqueous extract of Pimpinella anisum ameliorated the extent of renal damage induced by gentamicin. [13]

Histopathological examination of the kidneys of the GS group revealed the following: proximal tubular necrosis, vacuolation, desquamation, and degeneration of epithelial cells in the proximal tubules; hyaline casts in the tubular lumen; infiltration of mononuclear cells; and alterations in the glomerular and basement membranes.[14]

An aqueous extract of Carica papaya L. was administered prior to gentamicin exposure, significant disruptions of liver and kidney structures and alterations in biochemical parameters were averted. In summary, this research unequivocally established that applying an aqueous extract of *Carica papaya* L. before treatment with gentamicin effectively diminished the physiological and histopathological changes induced by the drug. In addition, new research avenues for the development of more effective therapeutic agents for liver, kidney, and other organ dysfunctions and diseases are identified in the present study.[15]

The increase in blood urea nitrogen (BUN) and serum creatinine was reduced in a dose-dependent manner when Tinospora cordifolia was administered to pre-treated groups. Histopathological observations bolstered the biochemical conclusions with additional evidence. The aqueous extract of *Tinospora cordifolia* has demonstrated nephroprotective properties when tested against gentamicin-induced nephrotoxicity [16]. Reducing oxidative stress, ferulic acid has consequently diminished the inflammation associated with GM-induced nephrotoxicity. The anti-inflammatory properties of ferulic acid have been highlighted in this study, as opposed to its antioxidant properties. Ferulic acid can mitigate nephrotoxic damage and exhibit kidney protective properties [17].

Acute renal injury was indicated by elevated serum concentrations of urea, uric acid, and creatinine, decreased levels of antioxidants, and proximal tubule necrosis and glomerular atrophy. Antioxidant supplementation markedly reduced serum urea, uric acid, creatinine, and antioxidant production in rats induced with GEN alone. Furthermore, antioxidant supplementation gave total cholesterol, free fatty acids, and triglycerides back to normal. These effects were all entirely reversible and linked to tubular necrosis caused by GEN. Our research indicates that antioxidants prevent the biochemical and histological toxicity of GEN by acting as a strong free radical scavenger in the kidney [18].

Serum creatinine, urine creatinine, and urine potassium levels significantly changed in the BA-treated group. The levels of urine sodium and chloride, as well as serum potassium, sodium, chloride, calcium, and phosphorus, did not change significantly ($P > 0.05$) in any of the three groups. Glomerular congestion, interstitial oedema, tubular necrosis, and interstitial haemorrhage were all less common in the BA-treated group. The results of this study indicate that BA decreases GM-

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induced nephrotoxicity, which may be related to the antioxidant, immunomodulatory, diuretic, and anti-inflammatory qualities of the medications. The exact mechanism by which BA protects the kidneys needs to be investigated further 19]. Allicin potentially retained nitric oxide levels in addition to its antioxidant, anti-inflammatory, and immunomodulatory properties, which may have contributed to its ability to protect against structural and functional damage caused by gentamicin. [20].The histopathological alterations in kidney tissue accompanied by oxidant and antioxidant status during gentamicin-induced nephrotoxicity, it can be concluded that date extract mitigates gentamicin-induced nephrotoxicity and protects the kidney. [21].

Plants have immense importance for humanity, as we use several plant species for medicinal purposes to prevent or cure various ailments [22,23]. In recent times, there has been a significant increase in the focus on natural products, especially medicinal plants, in pharmaceutical research [24]. Medicinal plants represent a valuable and widely accessible source of potential compounds for drug discovery. Many of the lead compounds in the pharmaceutical industry are derived from botanical sources. Date fruits are rich in polysaccharides such as pectin, and lignin. They are considered good sources of phenolic compounds, flavonoids, antioxidants, and anti-inflammatory agents; prevent bleeding; and are good sources of vitamins and minerals [25].

The plant, its variety, growing conditions, climatic and seasonal variations, geographical growth regions, degree of ripeness, growing methods, and numerous other factors, including postharvest treatment and processing, all affect the antioxidant properties of medicinal plants. Furthermore, the antioxidant effect is correlated with the makeup and concentration of currently available antioxidants, such as phenolic compounds. The assay methodology, solvent used, extraction technique, and conditions are crucial for accurately determining antioxidant capacity [26].

Antioxidant activities were comparable between dates gathered locally and those imported. A correlation between antioxidant activity and total phenolic and ascorbic acid was supported by evidence. Phenolics were identified as the primary source of antioxidant activity. [27].

Overall, it has been observed that water extract contains significantly higher concentrations of total phenol than alcohol, with Ajwa containing 455.88 mg/100g. [28].

There was a strong correlation (R2=0.975) between the antiradical efficiencies of the various varieties of date palm fruit (Phoenix dactylifera) from Algeria and their phenolic contents. It was discovered that all of the varieties mostly contained derivatives of cinnamic acid along with p-coumaric, ferulic, and sinapic acids. It was discovered that 5-o-caffeoylshikimic acid has three distinct isomers. Many forms of flavonoids, primarily flavones, flavanones, and flavonol glycosides, were discovered [29].

This study highlights the potential of Iranian dates as a good source of antioxidants that can be incorporated into functional foods. Investigations were conducted into the effects of sun drying and oven drying at temperatures between 50 and 80 °C on the phenolic compounds and AA of date palm fruits. TPC and AA varied with temperature and decreased with increasing drying temperature, as demonstrated by the drying process's results (from 667.3 to 610.5 mg galic acid in sun-dried dates of Mozafati and Kaluteh, respectively, to 314.2 and 210.4 in dried dates (80 °C) of Mozafati and Kaluteh, respectively). [30]. Date pits are a wasted resource even though they have a high phenolic and antioxidant content. The flesh and pits of ajwa dates may contain phenolics, antioxidants, and other nutrients, according to ethanobotanical records.Dietary fibers, fats. Studies on phytochemistry have revealed that the flesh and pits of ajwa are rich in specific flavonoids and phenolic compounds, which are potent antioxidants with a variety of health benefits for humans. Ajwa dates have potent biological effects [31,32].

Dates from Medina are among the varieties of date palms that grow in the Kingdom of Saudi Arabia and have high nutritional value due to their content of many major nutrients and important elements for nutrition [33,34]. The primary aim of the present study was to assess the possible nephroprotective properties of dates from Medina in experimental animals, specifically in the context of gentamicin-induced nephrotoxicity. This investigation sought to examine the protective effect of date fruit from Medina as a novel agent with potential nephroprotective properties.

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2. Materials and Methods

2.1. Chemicals

The chemicals employed were of analytical quality and utilized in their as-received state without undergoing additional purification processes.

2.2. Preparation of Date Fruit Extract

Date fruit was purchased from an herbal store in Riyadh, Saudi Arabia. An amount of 10 gm of date was extracted with 100 mL of distilled water at room temperature. The solution was then passed through a syringe filter and into vial, where it was prepared for injection into GC-MS equipment.

2.3. Gas Chromatography–Mass Spectrometry (GC-MS) Measurement

GC-MS analysis was performed using a Perkin Elmer Clarus 600 GC coupled with a mass spectrometer (Turbomass). A 1 µL extract volume was injected into an Elite5MS column, which possessed dimensions of 30 m in length, 0.25 µm in film thickness, and 0.25 µm in internal diameter. Injection was executed following the prescribed temperature protocol. The gas chromatography–mass spectrometry (GC-MS) system began by setting the initial oven temperature at 40 °C and keeping it constant for 2 min. Following this, the temperature was increased to 200 °C at a pace of 5 °C per minute, and this heightened temperature was maintained for an additional duration of 2 min. Commencing at an initial temperature of 200 °C, the temperature exhibited a linear progression at a rate of 5 °C per minute, ultimately attaining a final value of 300 °C. Following this, the temperature remained constant at this particular level for two minutes. The temperature of the injector was held constant at 280 °C. The temperature of the interface was measured to be 240 °C, although the source's temperature was recorded as 220 °C. The system's vacuum pressure was maintained at a magnitude of 1.11×10^{-5} torr, while the energy of the electrons was configured to be 70 electron volts (eV). In this experiment, helium was used as the mobile phase at a 1.0 mL/min flow rate. The mass spectra were obtained utilizing the electron ionization technique, with a scanning range from 40 to 600 m/z. Unidentified chemicals were discovered by comparing their spectra with those documented in the National Institute of Standard and Technology (2005) and WILEY (2006) libraries. The total time required to analyze a single sample was 58 min.

2.4. Experimental Animals

Thirty female Wistar albino rats weighing 150–200 gm (10–12 weeks old) were used during this research. The female Wistar albino rats were kept under standard conditions (temperature (25 °C)) according to the protocol approved by the university animal welfare committee (University of Gadarif, Sudan (1523)). The animals were divided into two major groups, prevention and treatment, and the prevention group was further divided into two groups. Group I rats (ten animals), as the control group, were given sterile normal saline intraperitoneally. Group II rats (ten animals) received GM at 100 milligram per kilogram intraperitoneally. Group III rats (ten animals) received date Ajwat Al- Medinah at 150 milligram per kilogram plus gentamicin orally for ten days. All samples were taken after the animals were sacrificed; samples included blood taken from the heart and sera, which were separated for biochemical tests, and kidney tissue for histopathological sections.

2.5. Biochemical Assays

An examination of renal function was carried out utilizing biochemical indicators, including blood urea levels, serum creatinine (SCr) levels, total protein, uric acid, and albumin.

2.6. Estimation of Total Phenolic Content

The total phenolic content of the samples was determined using the Folin–Ciocalteu reagent method. To measure the concentration of phenolic content (µg/mL) in the samples, a specific reagent

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was added to the samples, and the reaction's absorbance was quantified at a wavelength of 760 nm. To establish a calibration curve, gallic acid was employed as a standard for calibration.

2.7. Estimation of Flavonoids

Total flavonoids were extracted in a Soxhlet extractor with ethanol from powdered oven-dried date fruits (1 g). To the extract, 0.3 mL of NaNO2 (1:20) was added, followed by 0.3 mL of AlCl3 (1:10). After 6 min, 2 mL of 1 mol litre−1 NaOH was added. The absorbance was measured against a blank at 510 nm with a M8500 UV-Visible spectrophotometer (Taizhou Radio Factory).

2.8. DPPH Antioxidant Activity

DPPH was used to measure free radical scavenging. The assay was carried out according to Noman (2019). This test measures extract and fraction free radical scavenging. Extracts and fractions were tested at concentrations of 10, 50, 100, 500, and 1000 µg/mL. To create 1 mL of the test mixture, we mixed 500 µL of extract or fraction with 375 µL of methanol and added 125 µL of 0.04% DPPH ethanolic solution. An ascorbic acid positive control was used. Absorbance reduction was estimated at k = 517 nm after 30 min of room-temperature incubation in the dark. Scavenging action was calculated as follows:

$$\% \text{ of radical scavenging activity} = (\text{Abs control} - \text{Abs extract}/\text{Abs control}) \times 100$$

2.9. Histology and Light Microscopy

A histological examination was conducted to examine gentamicin's microscopic effects. The kidney was preserved and fixated in 10% formalin and embedded using paraffin. The section prepared for the stain was five-micron-thick. Hematoxylin and eosin stains (H&E) were used. A light microscope (Olympus/3H-Japan) was used for examining the specimens.

2.10. Statistical Analysis

The results were analyzed using the SPSS program (version 25), tested with ANOVA to compare data obtained from control groups and treated groups, and expressed as means ± SEMs (standard errors of the mean). The parentheses indicate a significant difference.

3. Results

3.1. Gas Chromatography–Mass Spectrometry (GC-MS)

The chromatograms of date fruit obtained using gas chromatography–mass spectrometry (GC-MS) are depicted in Figure 1. The data exhibit discernible peaks, indicating the presence of 20 identifiable chemical compounds. Table 1 displays the compounds and their respective gas chromatography–mass spectrometry (GC-MS) information. From the table, it can be seen that the percentage order of chemical compounds was as follows: n-hexadecanoic acid (29.69%) > diisooctyl adipate (11.83%) > eicosane (10.56%) > 2-nonacosanone (8.85%) > benzenepropanoic acid, 3,5-bis(1,1-dimethylethyl)-4-hydroxy-, octadecyl ester (7.26%) > phthalic acid, isobutyl octadecyl ester (4.61%) > 2-octadecyl-propane-1,3-diol (4.34%) > hexadecanoic acid, methyl ester (3.42%) > 13-tetradecen-1-ol acetate (2.99%) > 1,2-benzenedicarboxylic acid, diisooctyl ester (2.54%) > 1,2-benzenedicarboxylic acid, diisooctyl ester (2.53%) > octadecane (2.48%) > i-propyl 14-methyl-pentadecanoate (1.97%) > 9,12-octadecadienoic acid (Z,Z)- (1.68%) > heptadecane, 2,6,10,15-tetramethyl- (1.67%) > oxirane, hexadecyl-(1.46%) > 2-pentadecanone, 6,10,14-trimethyl-(1.03%) > 9-octadecenoic acid, (E)-(1.01%) > Z,E-3,13-octadecadien-1-ol (0.93%).

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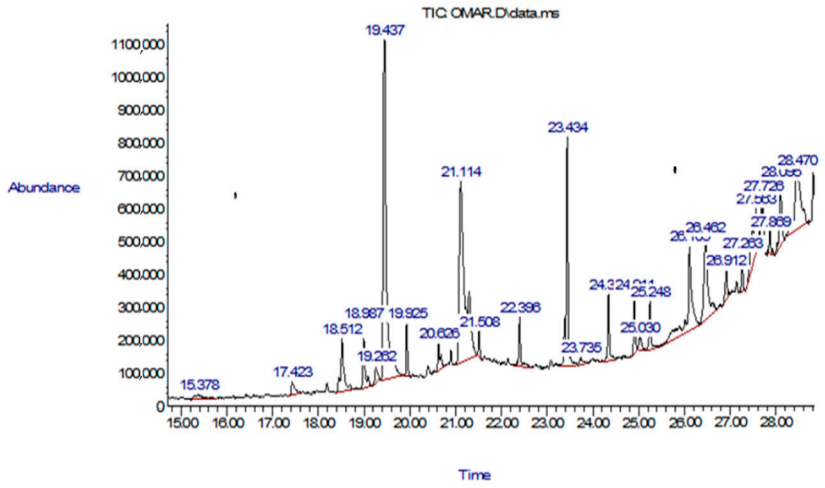

Figure 1. The chromatograms of date fruit obtained using gas chromatography–mass spectrometry (GC-Ms).

Table 1. GC–MS information of date fruit extract.

No.	Compound	RT (min)	Peak Area (%)	Mol Weight (amu)	Molecular Formula
1	Phthalic acid, isobutyl octadecyl ester	18.512	4.61	474.371	C30H50O4
2	Hexadecanoic acid, methyl ester	18.987	3.42	270.256	C17H34O2
3	9-Octadecenoic acid, (E)-	19.262	1.01	282.256	C18H34O2
4	n-Hexadecanoic acid	19.437	29.69	256.24	C16H32O2
5	i-Propyl 14-methyl-pentadecanoate	19.925	1.97	298.287	C19H38O2
6	9,12-Octadecadienoic acid (Z,Z)-	20.626	1.68	280.24	C18H32O2
7	Cycloeicosane	21.508	0.91	280.313	C20H40
8	Octadecane	22.396	2.48	254.297	C18H38
9	Diisooctyl adipate	23.434	11.83	370.308	C22H42O4
10	2-Methyl-Z-4-tetradecene	23.735	0.69	210.235	C15H30
11	1,2-Benzenedicarboxylic acid, diisooctyl ester	24.911	2.53	390.277	C24H38O4
12	Z,E-3,13-Octadecadien-1-ol	25.03	0.93	266.261	C18H34O
13	Eicosane	26.105	10.65	282.329	C20H42
14	2-Nonacosanone	26.462	8.85	422.449	C29H58O
15	Heptadecane, 2,6,10,15-tetramethyl-	26.912	1.67	296.344	C21H44
16	Oxirane, hexadecyl-	27.263	1.46	268.277	C18H36O
17	Benzenepropanoic acid, 3,5-bis(1,1-dimethylethyl)-4-hydroxy-, octadecyl ester	27.563	7.26	530.47	C35H62O3
18	13-Tetradecen-1-ol acetate	27.726	2.99	254.225	C16H30O2
19	2-Pentadecanone, 6,10,14-trimethyl-	27.869	1.03	268.277	C18H36O
20	2-Octadecyl-propane-1,3-diol	28.095	4.34	328.334	C21H44O2

3.2. Biochemical Assays and Histology Analysis

Gentamicin (GM) administration at a dosage of 100 mg/Kg caused stark nephrotoxicity, as proved by high serum creatinine and urea in blood, and caused severe kidney damage at the

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proximal convoluted tubules. Date fruit (Ajwat Al- Medinah) was given to animals for a protective effect against GM, and the results obtained were as follows: Serum albumin was 2.702 in the control; in the gentamicin (GM)-treated group, it was 4.032; and in the gentamicin plus date fruit (Ajwat Al-Medinah)-treated group, it was 2.488 mg/dl. Total protein was 4.89 in the control, in the gentamicin (GM)-treated group, it was 6.544, and in the gentamicin plus date fruit (Ajwat Al- Medinah)-treated group, 4.032 mg/dl. Uric acid was 2.946 in the control; in the gentamicin (GM)-treated group, it was 4.74; and in the gentamicin plus date fruit (Ajwat Al- Medinah)-treated group, it was 4.032 mg/dl. Urea was 58.58 in the control; in the gentamicin (GM)-treated group, it was 222.54; and in the gentamicin plus date fruit (Ajwat Al- Medinah)-treated group, it was 30.96 mg/dl. Finally, creatinine was 0.474 in control; in the gentamicin (GM)-treated group, it was 2.07; and in the gentamicin plus date fruit (Ajwat Al- Medinah)-treated group, it was 0.567 mg/dl.

The study showed that date fruit improved or lowered serum albumin, total protein, uric acid, urea, and creatinine and showed a good effect on the histology of the kidney tubules. Date fruit showed a significant effect in both prevention and treatment groups (Figures 1–6 and 9–11). Date fruit contained antioxidants; specifically, total phenolic content was 14 mg/gallic acid, and total flavonoid content was 32.22 mg/rutin equivalent. In addition, DPPH free radical scavenging in date fruit was 1000 ug/mL (Figures 7 and 8).

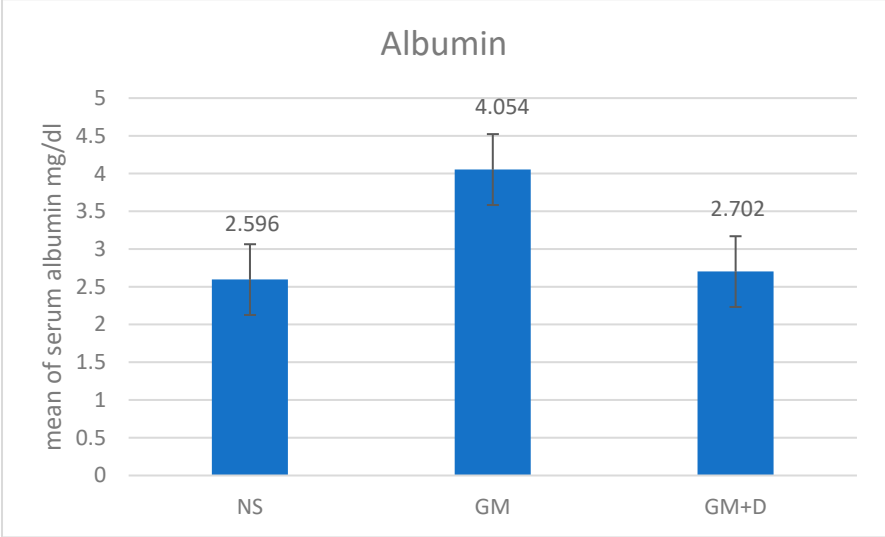

Figure 2. Means of serum albumin in prevention and treatment groups.

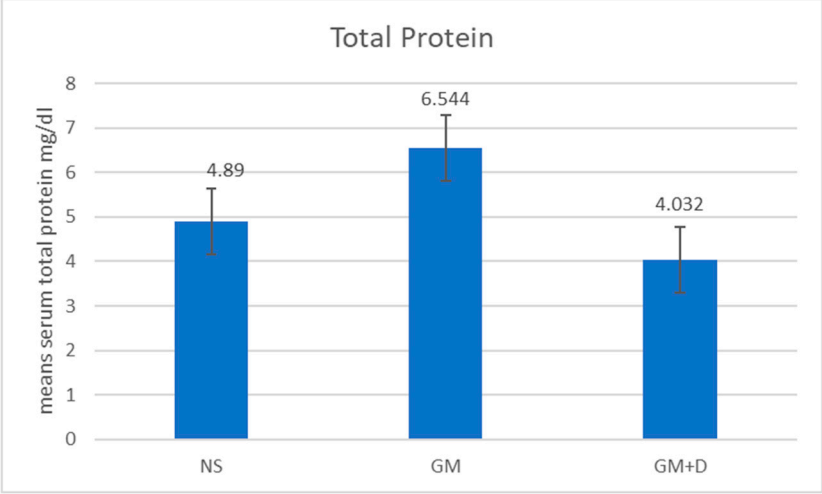

Figure 3. Means of serum total protein in prevention and treatment groups.

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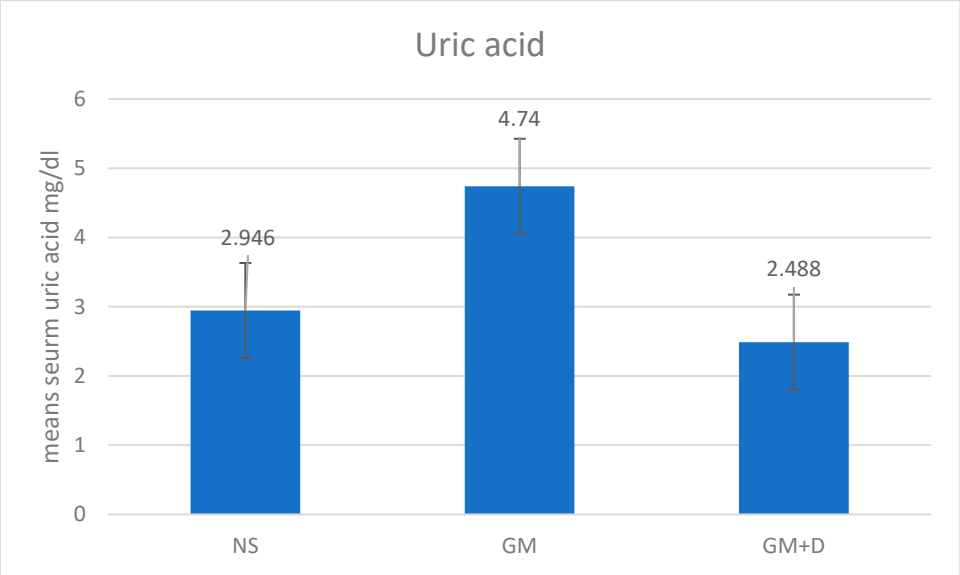

Figure 4. Means of serum uric acid (mg/dl) in prevention and treatment groups.

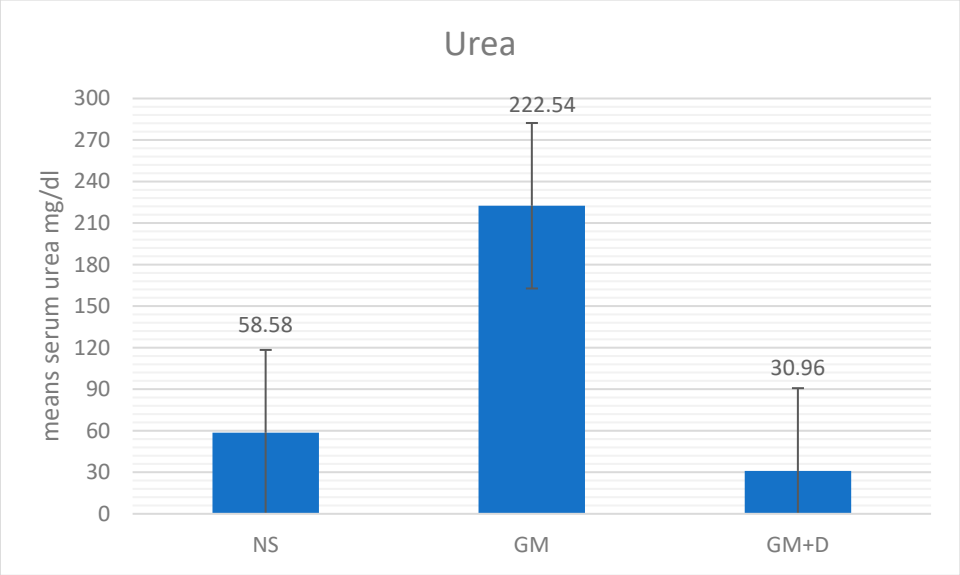

Figure 5. Means of serum urea (mg/dl) in prevention and treatment groups.

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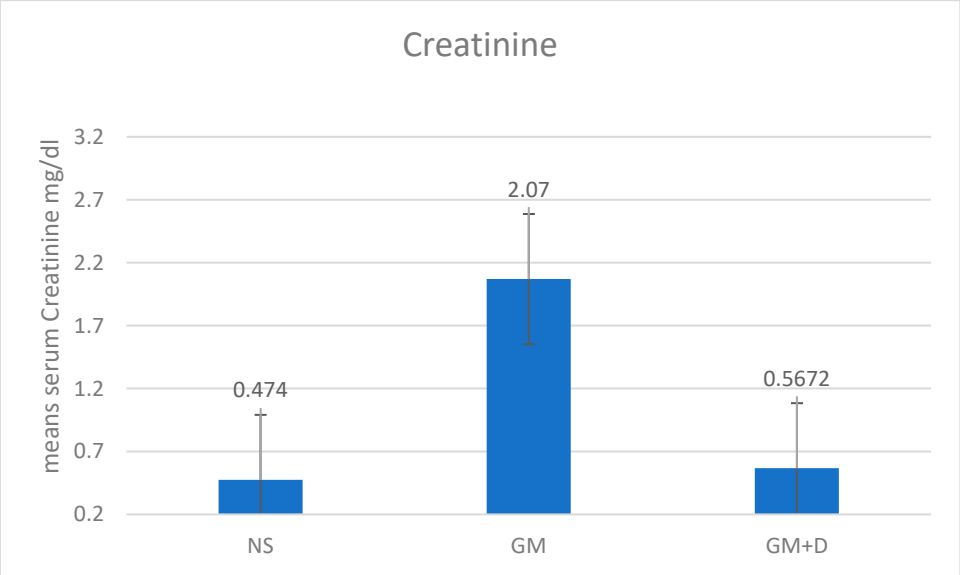

Figure 6. Means of serum creatinine (mg/dl) in prevention and treatment groups.

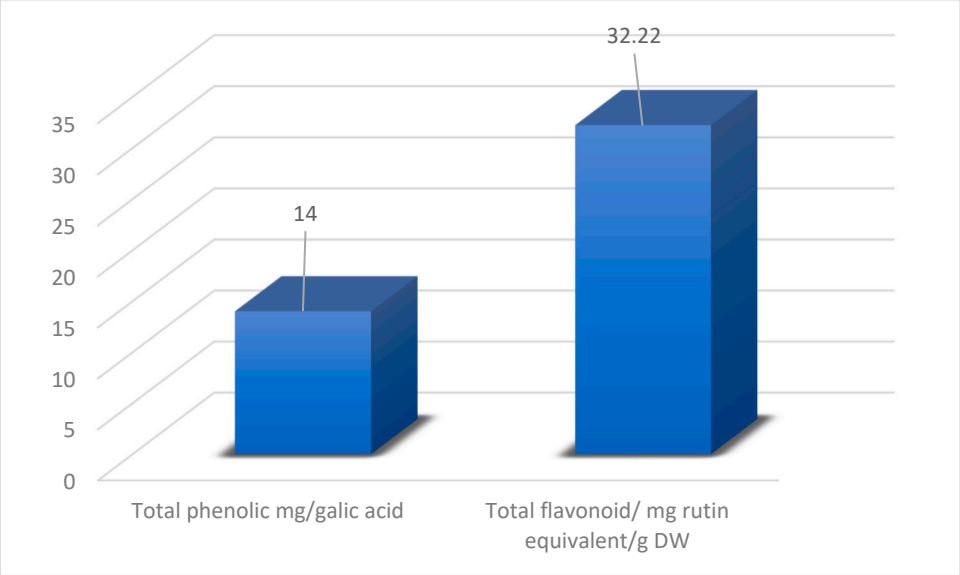

Figure 7. Means of total phenolic content (mg/gallic acid) and total flavonoids (mg/rutin equivalent/g DW) in date fruits.

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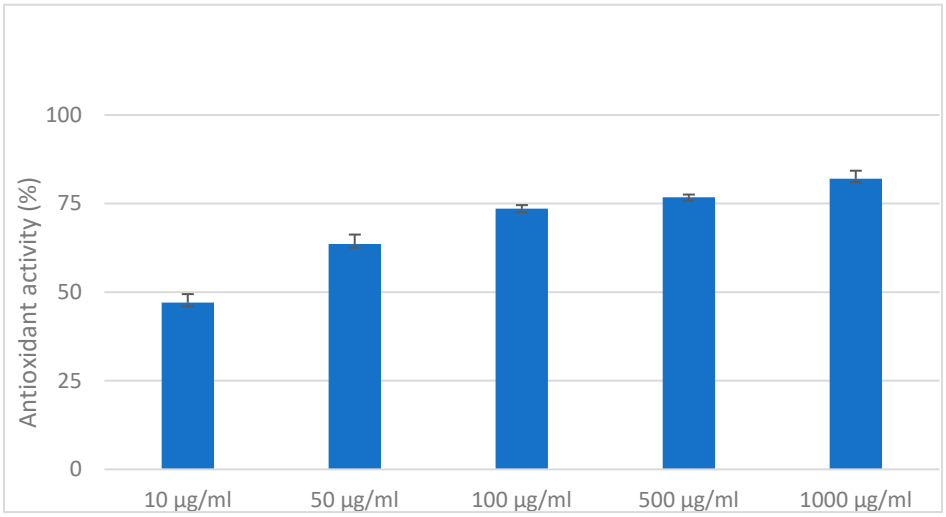

Figure 8. Antioxidant potential in date fruit extracts according to DPPH assay. Values represent % radical scavenging (AVG ± SD of three replicates).

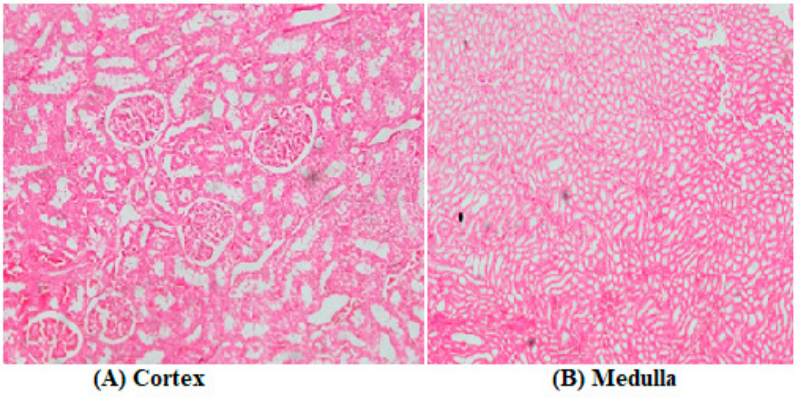

Figure 9. Microphotographs of histopathology of rat kidney show normal tissue in control and treatment groups (H&E X 200).

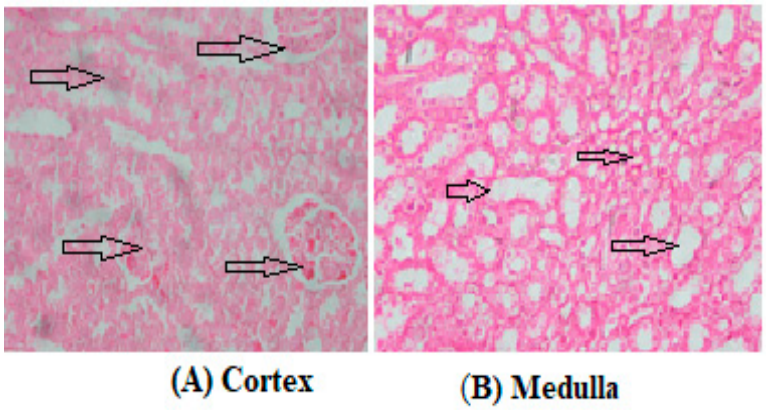

Figure 10. Microphotographs of histopathology of rat kidney show (arrows) dilatation of the renal tubule in the GM treatment group (H&E X 200) (H&E X 100).

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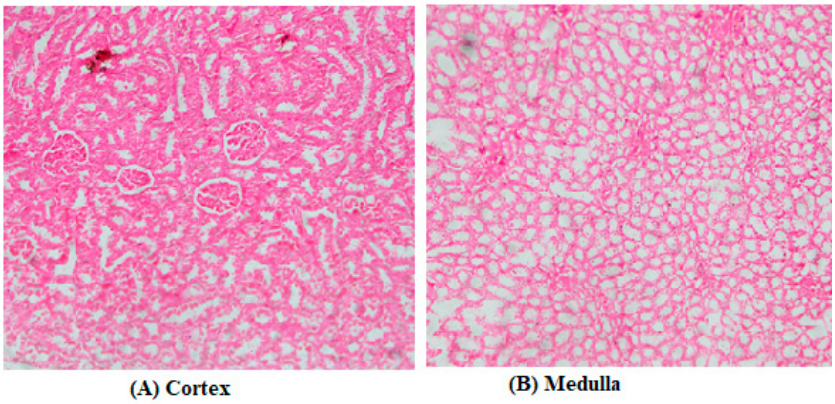

Figure 11. Microphotographs of histopathology of rat kidney show normal tissue in prevention and treatment groups (GM+D) (H&E X 200), showing slight recovery of tubules.

4. Discussion

There has been extensive research on the therapeutic benefits of secondary metabolites derived from date fruits in various biological systems. A wide range of disorders can be prevented and treated with the biological properties of natural substances such as flavonoids, alkaloids, phenolics, and tannins. The varied medicinal use of dates can be attributed to their phytochemical and nutritional constituents, such as polyphenols like gallic acid and flavonoids like quercetin. The hepatoprotective effects of gallic acid were shown in male rats, demonstrating the ability to alleviate liver damage generated by diclofenac. This was achieved through the modulation of oxidative stress and the suppression of IL-1β gene expression. Similarly, the compound quercetin has shown the ability to mitigate the harmful effects of diclofenac-induced liver damage by attenuating both the inflammatory response and oxidative stress. The results obtained in the current study are consistent with the result obtained by many researchers using amino acids as supplements or plant extracts to investigate their protective effect against GM-induced nephrotoxicity. A study used the amino acid L-arginine and found that GM significantly reduced serum levels of urea and creatinine in female rats [35]. In the current study, dates were shown to have high arginine content; this finding is supported by the results obtained by Alghamdi et al., who showed that ash and protein contents were the highest in Ajwat Al-Medinah [36]. The results obtained by gas chromatography-mass spectrometry (GC-MS) were supported by many researchers. Phthalic acid, isobutyl octadecyl ester is a bioactive compound [37], whereas hexadecanoic acid, methyl ester functions as an antioxidant, anti-inflammatory, antihyperlipidemic, and antimicrobial[38]On the other hand, 9-octadecenoic acid, (E)-, and n-hexadecanoic acid. The presence of these major phytoconstituents in date fruit provides a variety of biological activities such as antifungal, antibacterial, antioxidant, anti-inflammatory, and anti-tumor activity, which supports the plant's ethno-medicinal uses in disease curing [39]**,** i-Propyl 14-methyl-pentadecanoate also had antioxidant, antiandrogenic, antiproliferative, antieczemic, antihistamine, antibacterial, antifungal, hypocholesteromiic, and antitumor activity. The compound, 9,12-octadecadienoic acid (Z,Z)- [40]are predicted to be potent inhibitors of S. mansoni, P. falciparum, and T. brucei brucei survival, respectively. As a result, in vitro and in vivo bioassay studies on these compounds are required to establish the predictions[41]**.**Cycloeicosane has antioxidant, cytotoxic, antibacterial, anti-candidiasis, and in vivo anti-inflammatory properties[42]**.** Octadecane has been shown to reduce apoptotic cells [43]. Diisooctyl adipate has toxicological properties in biological fluids and tissues[44]**,** 1,2-Benzenedicarboxylic acid has shown promising results as a chemopreventive/chemotherapeutic agent against osteosarcoma[45]**,** diisooctyl ester, which has anti-oxidant and anti-inflammatory properties [46], Z,E-3,13-octadecadien-1-ol, which has antioxidant properties [47]**.**When eicosane exhibited higher antibacterial, antifungal, and antioxidant activity [48]**.**The heptadecane, 2,6,10,15-tetramethyl- , beneficial as a promising source of antimicrobial and antioxidant therapeutic agents [49], oxirane, hexadecyl- , ntimicrobial compounds [50]and benzenepropanoic acid phytochemicals with antimicrobial and anticancer properties [51], Hence, 3,5-

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bis(1,1-dimethylethyl)-4-hydroxy-, antimicrobial activities ([52],octadecyl ester, the promising inhibition efficiency of these compounds against the pathogenic bacteria [53]. The antimicrobial and antioxidant compounds [54], 13-tetradecen-1-ol acetate, and 2-pentadecanone, antioxidants [55], 6,10,14-trimethyl- 2-Octadecyl-propane-1,3-diol the findings suggest that fungal endophytes from the medicinal plant could be a potential candidate for bioactive compounds with pharmaceutical properties[56]

Many studies have used this plant as a preventive agent against GM nephrotoxicity and have obtained good results due to antioxidant content in plants [57,58]. Previous results support our findings, which indicate that date fruit has high contents of antioxidants and phytochemicals. Four different cultivars of date palm fruits famous in the KSA were investigated for phytochemical influence on experimental animals. The study found good impact on all parameters under study [59]. Antioxidant supplements were shown to mitigate the harmful impact on renal function caused by toxic agents [60]. The study found that some chemicals, such as ferulic acid, reduce the nephrotoxicity and damage caused by gentamicin. The remarks indicate that taurine treatment attenuates the effect of gentamicin on kidney tissue damage [61,62]. The addition of taurine attenuates oxidative stress related to renal damage by decreasing antioxidants in gentamicin-treated experimental animals. The reducing effect of royal jelly (RJ) was clear in groups given GM both before and after being given RJ, especially after, as it gave a better effect in terms of normalizing biochemical parameters, in addition to kidney histology [63]. All the above results support our findings, given the date fruit contents. Nutritional dates may have many health benefits. Phytochemicals in fruits prevent chronic diseases. Researchers and clinicians are interested in phytochemicals' antioxidant activity; cholesterol-lowering properties; and potential health benefits like cancer chemoprevention, diabetes prevention, and cardiovascular disease prevention [64,65]. Date fruit contains many carotenoids, polyphenols, tannins, and sterols [66]. Date variety, fruit-picking stage, storage, postharvest processing, geographical origin, and soil affect constituent concentration and composition [67]. According to several studies, date fruit chemical constituents and functional composition change dramatically during maturation, with sugar levels rising and fiber, mineral, and vitamin levels falling. Several experiments examined the overall carotenoid content in three different cultivars of date fruits (Al-Fard, Al-Khasab, and Al-Khalas). The findings revealed that Al-Khalas exhibited the highest concentration of carotenoids, which aligns with expectations due to its characteristic yellow hue. They also reported that the destruction of total carotenoids after the sun drying of date fruit ranged between 4 and 30% [68]. The TPC of all four varieties ranged from 32.24 mg to 35.84 mg caffeic acid equivalents/100 g of fresh weight. All varieties exhibited significant free radical scavenging activity (28.78-70.62%) in a concentration-dependent manner. The present study confirms that Omani dates are rich sources of phenolic compounds and possess good antioxidant properties. HPLC also revealed that gallic acid is the predominant phenolic acid in all date cultivars [69]. The content of rutin in Sukkari (8.10 mg/kg) was significantly higher than that in Ajwa and Khalas (6.50 and 3.60 mg/kg, respectively). However, the contents of catechin in Sukkari and Ajwa were equal (7.50 and 7.30 mg/kg), whereas in Khalas, it was significantly lower than in the latter varieties (5 mg/kg). On the other hand, there was no significant difference in the contents of caffeic acid between Ajwa and Sukhri, but it was higher in Khalas [70].

5. Conclusions

To sum up, the phytochemical analysis of date fruit is crucial to determining its chemical composition. The potential of date fruit to prevent gentamicin-induced renal nephrotoxicity was tested in female albino rats. The results showed that the 100 mg/Kg GM treatment caused abnormalities in kidney function and proximal convoluted tubule histology according to our tests. However, when the animals were fed Ajwat Al-Medinah dates along with GM, a preventive effect on GM-induced nephrotoxicity was observed. The serum albumin level in the control group was 2.702 mg/dl, while in the gentamicin treatment group, it was 4.032 mg/dl. However, when the rats were given date fruit along with GM, the serum albumin level decreased to 2.488 mg/dl, and the creatinine clearance and uric acid levels improved significantly. The study found that date fruit

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greatly affected the prevention and treatment of GM-induced nephrotoxicity. The combination of GM and date fruit fared the best in improving kidney function and histology.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of University of Gadarif, Sudan (under number 1523—15 July 2023). We used animals to try to find a solution to the side effects of gentamicin, which is associated with nephrotoxicity when used for treatment.

Informed Consent Statement: The abovementioned project was used laboratory animals has been revised and approved by the University " Animal-Welfare committee Body. according to University regulation, the project was reported to the Ministry of education Kingdom of Saudi Arabia, which granted approval under the implied consent rule.

Data Availability Statement: All data are available within the manuscript.

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